inducing a Th2 response.

Applicants wish to thank Examiner Lee and Supervisory Patent Examiner Lynette Smith for taking time to discuss the issues in this case in an interview with Applicants' agent on January 25, 2001. Applicants' response reiterates points raised by Applicants' agent during the interview.

Rejections Under 35 U.S.C. § 102(b)

The Examiner has rejected claims 24-32 under 35 U.S.C. § 102(b) as being anticipated by Kulberg, et al., 1992, *J. Immunology* ("Kulberg"). Applicants respectfully traverse the rejection. Applicants submit that the claims, as amended, require that a homogenate of a helminthic parasite preparation be separated into fractions, and that a fraction of the homogenate be assayed for the presence of a biological activity that reduces an excessive Th1 immune response. The specification provides support for this limitation at least at page 9, paragraph 6. The specification states that the term "fractionating" refers to the process of dividing a helminthic homogenate or a fraction of a homogenate into smaller sub-portions or fractions on the basis of some physical, chemical or biochemical property. Thus the specification clearly teaches that fractionating requires *homogenating and separating* components in a preparation.

In contrast, Kulberg describes studying the effect of a *Shistosoma mansoni* infection on an organism's immune response to a non-*S. mansoni* antigen, i.e., sperm whale myoglobin. Kulberg teaches exposing a mouse to *S. mansoni* antigens and then treating the animals 8 weeks later with myoglobin (page 3265). Kulberg provides the *S. mansoni* antigens in the form of an emulsified preparation of cercariae and eggs (Materials and Methods paragraph three). After antigenic challenge with myoglobin, Kulberg measures cytokines produced by the mouse. Kulberg does not teach producing a homogenate of a helminthic parasite preparation or fractionating the preparation and assaying the biological activity of individual fractions. Kulberg thus does not teach identifying specific components of the preparation responsible for reduction of a Th1 response.

Applicants note that during the interview of January 25, 2001, Supervisory Patent Examiner Smith acknowledged that the rejection of claims 24-32 over Kullberg was not appropriate in light of Applicants' proposed amendment (now amended claim 24). Applicants therefore respectfully request that the rejection be reconsidered and withdrawn.

Rejections Under 35 U.S.C. § 102(e)

Claims 24-31 have been rejected under 35 U.S.C. § 102(e) over U.S. Pat. No. 5,708,141 by Moyle, et al. ("Moyle") The Examiner asserts that Moyle teaches a method of screening for components which act as anti-inflammatory compounds while functioning as inhibitors of neutrophil activation. Applicants respectfully traverse this rejection. Applicants submit that Moyle, in fact, teaches fractionating a parasitic worm to obtain a specific component of a worm preparation, neutrophil inhibitory factor. Moyle then tests fractions for their ability to inhibit neutrophil adhesion and to inhibit hydrogen peroxide release from neutrophils.

As discussed in Applicants' previous Declaration under Rule 1.132 ("the 132 Declaration"), filed September 12, 2000; Moyle does not actually screen for an activity that reduces an excessive Th1 immune response because neither effects on neutrophil adhesion or inhibition of hydrogen peroxide release from neutrophils are associated with a reduction of an excessive Th1 response (see, generally paragraph 4 of the 132 Declaration, referring to Exhibit D, an article by Brown, which states that "neutrophils *do not* mediate the inflammatory effects of TNBS [which induces Th1 responses] and are not involved in the colonic response to PKC activation," and Exhibit E, an abstract by Melarange, which states that "neutrophils do not contribute to gastrointestinal ulceration and blood loss induced by nonsteroidal anti-inflammatory drugs....[thus] there is no evidence that neutrophils contribute to indomethacin-induced acute gastric erosion formation"). Further, as discussed in paragraph 4 of the 132 Declaration, neutrophils *do not* play a role in immunological diseases such as Crohn's disease, rheumatoid arthritis, or multiple sclerosis, and therefore a method of screening for modulators of neutrophil activity will NOT identify factors which reduce an excessive Th1 response.

The Examiner appears to be misled by a statement in Moyle that "compounds that modulate the function of neutrophils...have been shown to mitigate inflammation." However, Applicants respectfully submit that it is well known that inflammation is not *a priori* a Th1 response. Inflammation, as defined in Dorland's Medical Dictionary, is "a localized protective response elicited by injury or destruction of tissues which serves to destroy, dilute or wall off both the injurious agent and the injured tissue." On a macroscopic level, this is usually accompanied by the familiar clinical signs of erythema, edema, tenderness (hyperalgesia), and pain. However, Th1 cells, Th2 cells, and neutrophils can *all* mediate inflammation and each do so *in different ways.* For example, Th1 cells mediate inflammation by producing a set of characteristic cytokines such as interferon gamma (IFNg), interleukin (IL)-2, lymphotoxin (LT)a and granulocyte-macrophage colony-stimulating factor (GM-CSF), and Th1 responses are associated with cell-mediated immunity. Neutrophils also can cause inflammation, but do so through a different mechanism than Th1 cells. Neutrophils characteristically attach to the Fc portion of the immunoglobulin complex that forms for example, at a subcutaneous infection site, where they release digestive enzymes, causing visible acute inflammation. Thus, inflammation mediated by neutrophils is *not* an excessive Th1 immune response.

Applicants respectfully submit that it is irrelevant that Moyle suggests using neutrophil inhibitors to treat diseases such as inflammatory bowel disease and rheumatoid arthritis (col. 13, lines 15-35); the claimed method is not directed to identifying factors which modulate inflammatory diseases *using neutrophil inhibitors.* Further, Moyle is not enabling for a method of treating Th1 mediated inflammatory diseases, because Moyle provides no showing that neutrophil inhibitory factor has any effects on these diseases. It is well-settled in the law that a reference must be enabling for what it teaches. Because Moyle does not teach a method of screening a helminthic parasite preparation for components which reduce an excessive Th1 immune response, the reference does not teach all the elements of claims as required under Section 102. Therefore, in view of the above arguments, Applicants request that the rejection be reconsidered and withdrawn.

Rejection Under 35 U.S.C. § 103(a)

The Examiner has rejected claims 24-32 under 35 U.S.C. § 103(a) as being unpatentable over Moyle and Kulberg. The Examiner asserts that although Moyle does not expressly teach assaying a parasitic preparation *in vivo*, this deficiency is remedied by Kulberg. However, Applicants submit that, in view of the claim amendment and the above arguments, the combination of the teachings of Moyle and Kulberg do not yield the present invention. Further, because Moyle does not teach screening a helminthic parasite preparation for components that reduce an excessive Th1 immune response, one of skill in the art would not have been motivated to combine the teachings of Moyle with the *in vivo* assay taught by Kulberg. Applicants accordingly request that the rejection be reconsidered and withdrawn.

CONCLUSION

Applicants submit that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicants' agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned agent of record.

Respectfully submitted,

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Dianne Rees

Dianne M. Rees
Reg. No.: 45,281
PALMER AND DODGE, LLP
One Beacon Street
Boston, MA 02108
(617) 573-0100